Brain control of heart regulation

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Chapter 5

Integration, correlations, and conclusions

The last chapter of this thesis consists of three parts. The first part offers an integrative discussion of the phasic cardiovascular and cortical results. In the second part the correlations between the cardiovascular and the cortical results are investigated, and the third part of this chapter lists the main findings and conclusions of the present study.

5.1 Integration

This section first gives a short review of the experimental manipulations used in the experiments, and the main cardiovascular and cortical results. Then, a theoretical framework is presented which appears appropriate for integrating these results. Subsequently, a short discussion follows about the autonomic origin of the phasic cardiovascular responses.

5.1.1 Review of manipulations and results

Three major experimental manipulations were used in the experiments; memory load, response instruction, and knowledge of results.

First, the amount of processing required by the task at S1 was varied. In Experiment 1 the memory set consisted of two or five letters. The results of this easy/difficult manipulation showed that heart rate (HR) and blood pressure (BP) can react differentially to the same experimental manipulations: there was a striking effect of the load manipulation on the components of the BP response, whereas there was no effect on the HR components. The difficult memory search condition enhanced the latency and amplitude of the initial BP decrease, and attenuated the subsequent maximum. It was concluded that the initial changes in the BP-pattern are related to input processes, i.e. intake of the presented material,

and processing of its information content (see section 3.1.2). The positive slow wave (PSW) and the prolonged parietal positivity (NSW latency range) were attenuated in the difficult condition.

In the other experiments the experimental conditions were compared to a simple reference task; the latter did not require memory search. In the reference condition of Experiment 2 the intermediate HR- and BP-increase had disappeared. Since the same stimuli were presented as in the experimental conditions, but with the instruction to ignore the response instruction attached to these stimuli, it was concluded that the absence of a memory search requirement was responsible for the absence of the increase of HR and BP. This result is in line with Experiment 1 in that the early components appear to reflect the processing of the information content of S1. Furthermore, the explicit instruction that a speeded response was not required in the reference condition may have lowered the impact of S1, compared to Experiment 3. In the latter experiment, the reference condition required a speeded response, and a clear triphasic pattern of evoked HR and BP was found in spite of the absence of memory search.

In line with the effects of Experiment 1 the PSW was larger in the reference condition (less processing required) than in the experimental conditions. However, the prolonged parietal positivity was virtually absent in the reference conditions of both Experiment 2 and Experiment 3. This shows that the effects on the PSW and NSW (prolonged positivity) are independent. It was concluded that the PSW appears to reflect the identification and initial processing of the stimulus (i.e. stimulus perception and identification), whereas the NSW seems more related to further processing. In all experimental conditions of the three experiments, this further processing consisted of searching the letters held in memory and comparing them with the letter presented at S1. In the reference conditions there was no memory search task, and therefore no additional processing was required which explains the absence of the prolonged parietal positive slow wave.

The memory load manipulations were expected to affect the early components of the cardiovascular and the cortical responses. Indeed, the effects were found on the first and second components of the cardiovascular responses (initial decrease and subsequent increase), and on the slow waves occurring early in the S1-S2 interval (PSW and NSW).

The second major manipulation was the response instruction. In all three experiments the response instruction in the experimental conditions was to give either a fast or a delayed response. Furthermore, in the reference condition of Experiment 2, the instruction was to respond within one second after S2, but without stress on speed. In contrast, in Experiment 3 the reference task required a speeded response. The effects of the response instruction were expected to be found in the later components of the cortical and cardiovascular responses. Indeed, most effects are found on HR-D2, BPmin2, and the contingent negative variation (CNV). In Experiments 1 and 3, the latencies of HR-D2, SBPmin2, and DBPmin2 were longer after the instruction to give a delayed response. In

Experiment 2 this was only found for HR, which was attributed to the smaller number of subjects in that experiment. The CNV was larger when a fast response was required. In Experiments 1 and 3 the response instruction also affected HR-A and BPmax; their latencies were longer when a delayed response had to be given. It was concluded that the late cardiovascular (HR-D2 and BPmin2) and cortical (CNV) components reflect the preparation of the motor response. The effects on the preceding components indicate that the preparation started quite early in the S1-S2 interval.

The third major class of manipulations involved the feedback about the performance, or knowledge of results (KR). In Experiment 1, the neutral KR with no reward was contrasted with noise KR, where aversive noise was presented whenever an incorrect response was given. In the neutral KR condition the decreases in the HR and BP patterns were smaller and the increases larger. Also a smaller NSW was found with neutral KR. In Experiment 2 the KR manipulation involved reward in both conditions: the reward was either positive (money) or negative (noise). The noise condition induced larger overall changes in the evoked HR and BP patterns, and resulted in less errors and faster responses. In Experiment 3, the Control condition consisted of KR with reward, and the NoControl condition had no KR but did have a negative, aversive noise, 'reward'. The initial changes in the HR and BP patterns were larger in the KR-with-reward (Control) condition. The NoControl condition caused longer latency of the late cardiovascular changes, a larger NSW, and caused more errors (when a delayed response was required).

The KR manipulations were intended to affect the motivational and/or emotional state of the subjects, to enhance the cardiovascular changes, and to cause lateralization of the cortical slow waves. The first of these intentions is hard to evaluate; the subjects' reactions to the KR manipulations differed enormously. As Damasio (1994) pointed out, what some subjects consider as 'absence of punishment' is perceived as 'reward' by others. In the present study, particularly during Experiment 3 these personal differences became very clear. About half of the subjects preferred the NoControl condition, which let them 'just do their jobs', over the information overload (as they perceived it) provided by the Control condition. On the other hand, a large part of the remaining subjects displayed signs of distress after having performed the NoControl condition; these subjects clearly had felt out of control. It is very unfortunate that these personal reactions have not been noted more consistently, which makes it impossible to make a post-hoc analysis of possible differences between these groups of subjects.

The second intention of the KR manipulations was to enhance the cardiovascular effects. It is not clear whether this has actually happened. Although in Experiment 2 there was a large difference between the evoked HR and BP patterns in the positive and negative reward condition, this difference consisted of a shift of the entire patterns, and not of an enhancement of the individual components.

The third intention, lateralization of the cortical slow waves, was not realized. No consistent lateralization was found. Apart from the reason mentioned above, the large individual differences, this may be due to the difficulty of inducing real changes in emotional state by using such tasks as presently used. Probably the effects of feedback (KR) that were found were due to changes in motivation (reward; the possibility to earn money). In most investigations involved with emotion-induced lateralization, specific 'emotional' stimuli were used such as pictures of mutilated bodies or other unpleasant sights (e.g. Klorman & Ryan, 1980). In the present study possibly the only 'emotion' which may have been induced is frustration. Furthermore, in many studies investigating emotion-related cortical asymmetry, general activity measures such as spectral power or alpha-activity are used instead of event-related potentials (e.g. Ahern & Schwartz, 1985; Meyers & Smith, 1987; Davidson, Chapman, Chapman, & Henriques, 1990).

In order to give an interpretation of the results in a larger perspective, the theoretical distinction of three attentional control systems made by Pribram & McGuinness (1975) is used. The next section shortly introduces the mechanisms, and the subsequent sections discuss the experimental results in the light of this theoretical framework. Figure 5.1 gives a schematical integrative overview of the ideas presented in this section.

5.1.2 Attentional control mechanisms

The cardiovascular and cortical components which were used in the present study appear to fit perfectly in the attentional control systems recognized by Pribram & McGuinness (1975). They presented a model which consists of two systems, arousal and activation, which are coordinated by a third system, effort. Arousal and activation are assumed to be involved with input and output processes, respectively.

Arousal Arousal is described by Pribram & McGuinness (1975) as 'the registration of input in awareness', and deals with sensory processing and perceptual encoding of the presented stimulus. Arousal is assumed to be controlled by the amygdala and related frontal cortical systems. Two amygdala circuits are distinguished: one is a facilitatory frontal–amygdala–lateral-hypothalamic circuit, the other is an inhibitory orbito-frontal–amygdala–medial-hypothalamic circuit. The reciprocal action of these circuits facilitates fine-tuning of arousal. Both circuits are assumed to operate on serotonergic neurons in the brain stem. Norepinephrine (NE), however, is also mentioned in relation with arousal. Tucker & Williamson (1984) cite evidence that the NE-system has been shown to be responsive to novel environmental stimuli, which supports perceptual orienting. The arousal system is then comparable to the orienting reaction. The two neurotransmitters (i.e. serotonin and NE) should reciprocally support the brain's responsivity to perceptual input (by maintaining a certain level of arousal). Noradrenergic cells

in the brain are found in many brain areas, but relatively large concentrations of cells are found in the locus coeruleus (LC) in the dorsolateral pons, and in the A5 cell group in the rostral ventrolateral medulla (RVLM). It should be noted, however, that although there are many central noradrenergic neurons, it is not clear whether or how their functioning is directly related to cardiovascular control (Guyenet, 1990). A relation between NE-systems and arousal is that when during sleep, when externally oriented attention is not present, the LC shows low levels of activity. Furthermore, in wake animals activity of the LC seems to be related to the animals' behavior: LC activity decreased when the animal engaged in inwardly turned behavior such a grooming (Tucker & Williamson, 1984).

Serotonin is found in the caudal raphe nuclei (nucleus raphe pallidus and nucleus raphe obscurus), and in the dorsal motor nucleus of the vagus nerve (DMV). Guyenet (1990) cites evidence that serotonin is a neurotransmitter in the intermediolateral cell column (IML), the main sympathetic pathway (see also Chapter 1). He hypothesizes that the inactivity of serotonergic neurons in the raphe nuclei during REM sleep could contribute to the reduction of arterial blood pressure during that sleep stage. He furthermore indicates a general role of raphe serotonergic neurons in the modulation of central nervous system activity in relation to states of vigilance. In all, the evidence brought forward by Guyenet (1990) relates serotonin activity to the sympathetic system as well as to arousal. Parmeggiani & Morrison (1990) also cite evidence for serotonergic control of sympathetic activity; the dramatic decrease of sympathetic tone found during REM sleep, accompanied by low HR and BP, could also be induced by stimulation of the nucleus raphe obscurus. Thus, the cited evidence so far suggests that arousal mechanisms are mainly reflected in sympathetic changes, which appear to be related to activity of serotonergic and noradrenergic neurons. Frank & Smith (1990) stated that an increase in the central activity of serotonin may reduce the sympathetic activity from the brain to the heart. They consider serotonin activity as a possible mechanism that prevents harmful sympathetic outflow to the heart. Furthermore, Loewy & Spyer (1990) showed that the nucleus ambiguus (NA) has a concentration of serotonin receptors, and stated that serotonin, "... alone or coliberated with another transmitter, is a probable transmitter regulating cardioinhibitory activity." The NA is a nucleus with large efferent vagal projections to the heart. This implies that arousal or input related activity is at least capable of mediating both vagal and sympathetic changes in HR.

Relating the arousal concept to the experimental manipulations reviewed above, it may be expected that the effects of memory load, which manipulates input processes, are found on the same components that are sensitive to changes in arousal. Thus, changes in arousal, like changes in memory load, might affect the early components of evoked HR and BP (initial decrease and subsequent increase), as well as the initial cortical slow waves (PSW and NSW). The cardiovascular effects may originate from changes in vagal as well as sympathetic activity. This latter topic will be further discussed in section 5.1.3.

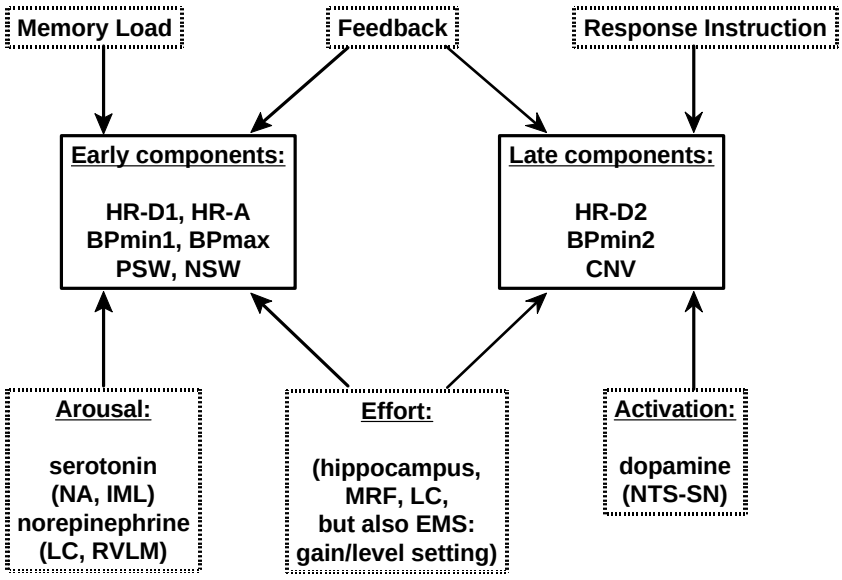

Figure 5.1: *Schematic representation of found effects and hypothesized underlying mechanisms. NA = nucleus ambiguus, IML = intermediolateral cell comlumn, LC = locus coeruleus, RVLM = rostral ventrolateral medulla, MRF = mesencephalic reticular formation, EMS = emotional motor system, NTS = nucleus of the solitary tract, SN = substantia nigra.*

Activation According to Pribram & McGuinness (1975) activation is related mainly to output processes, both perceptual (expectancy) and motor (readiness). It maintains a 'tonic' readiness for action, with tonic being in the order of seconds or longer. The CNV is mentioned as a typical example in reflecting activation. Activation reflects an action mechanism controlled by the basal ganglia, and is involved in dopaminergic (DA) systems of neurons which connect the substantia nigra (where many dopaminergic neurons are located) with the basal ganglia. Dopaminergic systems have been shown to facilitate the selection of specific motor acts and to determine the sequence in which they have to be performed. DA-neurons in the substantia nigra (SN) receive projections from the nucleus of the solitary tract (NTS) (Loewy, 1990), which, as reviewed in Chapter 1, is considered to be the cardiovascular control center. Apart from involvement in motor processes, dopamine also appears to mediate reward (Loewy & Spyer, 1990). However, Loewy & Spyer stated that the latter effects could also have been due to a change in motor functions.

The late components in evoked HR and BP (i.e. HR-D2, SBPmin2, and DBPmin2), as well as the CNV are related to output processes. The activation concept may thus be relevant in interpreting the effects on these components.

The distinction between input and output processes, reflected in early and late components of the evoked cardiovascular responses, respectively, bears a strong link with the dissociation between the early and late components of cortical and autonomic responses observed by Rockstroh & Elbert (1990). They linked the early changes in both autonomic (HR-deceleration, D1) and cortical measures (early negative slow wave; NSW), since they are not only found in two-stimulus paradigms, but after presentation of single stimuli as well. In contrast, the late components develop during the anticipation of an event (stimulus or response).

Effort Pribram & McGuinness (1975) noted that in some circumstances, there is a coupling between arousal and activation. To avoid endless circling in arousal (input)–activation (output) sequences, where the perception of the output action serves as new input, there should be a coordinating system which allows uncoupling of arousal and activation, for instance by habituation. Effort is such an intermediate process. It is controlled by a hippocampal circuit, which involves the Papez circuit (hippocampus–hypothalamus–cingulate gyrus–hippocampus). This circuit was first assumed to be involved in emotions, but later appeared to be more important in memory (Martin, 1989; LeDoux, 1996). Nevertheless, the hippocampus appears to have a connection with emotion, in that its task is considered to create a context in which memories are placed (see LeDoux, 1996).

The concept of effort, in coordinating the balance between arousal and activation, may be able to change the level setting, or general reactivity of different physiological systems. Pribram & McGuinness (1975) described two systems that influence the hippocampal circuit. The first is located in the raphe nuclei and associated structures in the mesencephalic reticular formation (MRF), and the other system is located more laterally in the locus coeruleus (LC) and other portions of the central (or periaqueductal) gray (PAG). The LC has an important noradrenergic pathway to the median forebrain bundle and other portions of the limbic system. These structures are also involved in the so-called emotional motor system (EMS), put forward by Holstege (1991).

The EMS is a third motor system, which exists besides the first (consisting of premotor projections to motoneurons) and second (the somatic motor system) systems. It represents the limbic component of the motor system. The lateral part of the EMS is effective via the premotor interneurons of the first motor system, and mediates specific emotional behaviors. This part of the EMS originates laterally in the limbic system, e.g. in the lateral hypothalamus and the central nucleus of the amygdala. These two areas project to the PAG, and stimulation of these areas can induce cardiovascular responses (Jordan, 1990; LeDoux, 1996). The medial part of the EMS regulates gain and level setting systems; this part has projections to the LC, and is able to change the general level of activity of the somatosensory and motoneurons by changing the excitability of their membranes (Holstege, 1991).

Thus, neuroanatomical (EMS) as well as psychological (effort) evidence suggests that the general level setting of certain regulatory systems may be affected by emotion-related processes. It may be possible that the effects of the feedback (reward) manipulation as found in Experiment 2 were caused by such an effort related change in level setting.

5.1.3 Autonomic origin of phasic cardiovascular changes

In the previous section it was implied that both the vagal and the sympathetic part of the autonomic nervous system may be involved in arousal. Furthermore, arousal was related to input processes; the effects of the memory load manipulations were mainly found on the initial components in the cardiovascular and cortical patterns. These data lead to the question where the phasic cardiovascular changes stem from in terms of autonomic origin.

The evoked HR pattern is mostly thought to be of vagal origin. For instance, Obrist, Wood, & Perez-Reyes (1965) showed that vagal blockade (through intravenous administration of atropine) caused significant reduction of both cardiac acceleration (HR-A) and deceleration (D2). They used an S1-S2 paradigm where the interval between S1 and S2 was 7 seconds. It should be noted that in both the unblocked and the blocked conditions, no initial HR deceleration was found, and that Obrist et al. (1965) considered the accelerative response as a respiration artifact. Furthermore, they stated that the baseline level of HR was greatly elevated in the blocked condition, which they held at least partly responsible for the smaller responsivity. Since no absolute HR levels are shown, this makes the effects hard to evaluate. Somsen, van der Molen, & Orlebeke (1983) found no effect of sympathetic blockade on the morphology and amplitude of the cardiac response in a 5-second S1-S2 interval. They gave human subjects either a dosage of propanolol or a placebo, and let them perform five different conditions. In each condition, the evoked HR response consisted of the triphasic D1-A-D2 pattern. Although the amplitudes of the peaks differed considerably between the conditions, no differences were found due to the blockade except for a lowered baseline level of HR during sympathetic blockade. This would imply that HR acceleration is caused by vagal inhibition, since during (total) sympathetic blockade only vagal activity can affect HR.

In contrast, in a more recent investigation Quigley & Berntson (1990) showed evidence (in rats) that only the initial changes in HR were merely vagal, and the changes occurring later on were affected by the sympathetic system as well. Quigley & Berntson (1990) did not use an S1-S2 paradigm, but presented auditory nonsignal stimuli of one second duration at intervals of 30 seconds. In response to these stimuli, the rats showed clear deceleration-acceleration HR responses. Vagal blockade (by administration of scopolamine) eliminated the deceleratory HR responses and appeared to unmask the acceleratory response; the BP response was not affected by vagal blockade. Sympathetic blockade (with atenolol) reduced the

cardiac acceleration, and enhanced the deceleration. Quigley & Berntson (1990) concluded that the cardiac acceleration appears to result from sympathetic activation, and the (initial) deceleratory response has a vagal origin. Computer simulation studies by van Roon (in preparation) and Van der Veen (1997) also indicated that the initial changes in HR could not be caused by changes in sympathetic activity, but by vagal changes only. Changes in HR and BP which occur with a latency of at least a few seconds could be due to sympathetic as well as vagal changes.

Combining these results, this would imply that HR-D1 is vagally mediated (Quigley & Berntson, 1990), since it occurs too soon after S1 to be mediated sympathetically. Cardiac acceleration could be caused by vagal inhibition (Somsen et al., 1983), or by an increase in sympathetic activity (Quigley & Berntson, 1990). The results of Quigley & Berntson appear to favor the latter option, through their option of coactivation of vagal and sympathetic activity; whereas the increase in vagal activity regulates the deceleratory changes, a short impulse of sympathetic activity causes an intermediate acceleration. HR-D2 may be either vagally mediated (Obrist et al., 1965), or caused by a combination of vagal and sympathetic activity (Quigley & Berntson, 1990; van Roon, in preparation; Van der Veen, 1997).

5.1.4 Discussion of results

Memory load The different cardiovascular patterns in the two reference conditions (i.e. mainly decelerative in Experiment 2 versus clearly triphasic in Experiment 3) may be caused by the impact of the S1 stimulus. No memory search was required in the reference conditions, and S1 was merely a warning that six seconds later a response had to be given. The difference was, however, that in Experiment 2 there was no stress on speed, whereas in Experiment 3 a speeded response was required after S2. This difference caused S1 to have a larger signal function, with more impact, in Experiment 3 than in Experiment 2. Larger HR acceleration after stimuli with higher intensity/impact relative to low-impact stimuli was found by Coles & Duncan-Johnson (1975) and Connor & Lang (1969) as well. Quigley & Berntson (1990) also found that HR-acceleration was larger after a high intensity stimulus, and found that this acceleration diminished after sympathetic blockade. Thus, the high-impact stimulus appeared to induce a sympathetic increase of HR, whereas after the presentation of a low-impact stimulus the HR acceleration is largely obscured by vagal decrease of HR. This implies that both sympathetic and vagal activity are enhanced: Coactivation of vagal and sympathetic activity occurs when the stimulus impact is low, whereas during high intensity stimulation there is a short sympathetic predominance which causes an enhanced cardiac acceleration. When applied to the present results, this implies that in Experiment 2 the absence of HR-A and BPmax is due to the smaller increase in sympathetic and/or larger increase in vagal activity.

Based on these results and on the neurophysiological evidence presented earlier, the input related processes involved in processing the information content (or 'meaning' in a broad sense of the word) appear to evoke mainly sympathetic nervous activity. Earlier input processes, such as the perception of the stimulus, may be vagally reflected in the initial cardiac deceleration. This would be in agreement with the notion that arousal may affect both vagal and sympathetic activity. The positive slow wave (PSW), which is assumed to reflect the initial processing of the stimulus material, should then be associated with the initial cardiac deceleration, whereas the negative slow wave (NSW), which is assumed to reflect the further processing of S1, should be associated with cardiac acceleration. This 'further processing', which results in enhanced sympathetic activity, leads to changes in BP as well as HR. However, HR is under vagal control as well, and since the vagal effects on HR are more powerful than sympathetic changes, the HR pattern cannot differentiate between the sympathetic and vagal effects of arousal. Thus, it appears that the sympathetic effects on HR are masked by the vagal effects initiated earlier.

Response instruction The peaking of the second HR deceleration (D2) at about the time the response is given indicates a close connection with motor activity. The amplitude of the CNV, which is mostly seen as an indication of response preparation (see Rohrbaugh & Gaillard, 1983), was larger after the instruction to give a fast response. Both the cardiovascular and the cortical results were thus in accordance with the literature (Brunia & Damen, 1985; Putnam, 1990; Gaillard & van Beijsterveldt, 1991; Otten, Gaillard, & Wientjes, 1995).

Activation, the attentional control mechanism related to output processes, is assumed to maintain a 'readiness for action' (Pribram & McGuinness, 1975). Pribram & McGuinness (1975) themselves indicated the connection between activation and the CNV, which they assumed could either reflect expectancy or motor readiness. It is clear that the present results indicate a larger readiness when a fast response is required. Of course, it is reasonable to expect that the maximum preparation of a delayed response is postponed until just after S2. The CNV results (i.e. the indicator at the fixed period immediately before S2) indeed show that preparation is not yet optimal when a delayed response is required. The HR (and BP) results (i.e. the indicators of the maximum negativity 'regardless' of time) also confirm the delay of maximum preparation when a delayed response is required.

Based on these results, it may be expected that there is a relation between the CNV and HR-deceleration. Relations between HR deceleration and the CNV have been implied by a number of authors (e.g. Connor & Lang, 1969; Lacey & Lacey, 1970; Simons, 1988). However, significant correlations have been presented only sporadically (see for an overview section 5.2.1). The problem with relating the CNV and HR-D2 may be due to the way these components are measured.

Whereas the CNV is mostly measured immediately before S2, thus at a fixed position in time, the HR-D2 is often measured at a variable time, depending on the maximum deceleration. This difference might cause dissociation.

Knowledge of results Manipulating feedback, or knowledge of results, often aims at motivating the subjects to increase their performance. This improvement can be accomplished by affecting either arousal, and thus the processing of input information, or activation, thus the output. The third possibility is that effort is affected, which may lead to overall changes in the pattern of reactivity, including both input and output processes. In the previous section it was shown that effort may affect the level setting of regulatory mechanisms. Steyvers (1991) investigated the effect of KR in a number of sleep-deprivation studies. The presentation of KR, even without a reward, increased the subject's motivation to perform by offering an evaluation of his performance. Although not all his results were convergent, Steyvers (1991) hypothesized that the effect of KR may, at least partly, be a compensation for a lack of arousal through mobilization of effort. Most of Steyvers's (1991) results did indicate that KR does not affect activation.

The pattern of HR and BP changes in Experiment 1 (i.e. noise induced larger decelerations/decreases and smaller accelerations/increases) appear to indicate a smaller vagal effect and/or a larger sympathetic activity in the neutral KR condition. Thus, both the HR and the BP pattern appear to have shifted toward larger negativity in the noise condition; relatively more vagal and/or less sympathetic activity. As was hypothesized in section 3.1.2, neutral KR, particularly in combination with low memory load, may have caused the task to be rather boring. This may have resulted in a decline of arousal, which had to be compensated for by more effort.

The changes in Experiment 2 showed a rather different effect; although in the negative reward condition the HR pattern was less decelerative, the BP was more decreased. Thus, instead of having results in the same direction, as in Experiment 1, the changes in HR and BP are opposite. The enhanced HR-A in the negative reward condition might be caused by a larger sympathetic activity, but this is in contrast with the larger decrease in BP occurring at the same time. Perhaps this is not merely a sympathetic, but a vagal effect. This effect may well be due to a temporary change in the level setting of the baroreflex, induced by an effort mechanism.

In Experiment 3 the Control condition, in which KR was presented, improved performance, and caused shorter latencies in the cardiovascular responses. On the other hand, the absence of KR in the NoControl may have caused timing uncertainty, and thus required additional evaluation of the stimulus in order to facilitate timing; this process may be reflected in the NSW.

In summary, the effects of KR appear to be related to effort, albeit differently in the different experiments. The results of Experiment 1 suggest that effort was

mobilized to compensate for arousal, whereas in Experiment 2 effort appears to have induced a change in level setting of the baroreflex.

5.2 Cardiovascular-cortical relations

One goal of this thesis was to examine the relationship between cardiovascular and cortical changes. In the literature relations have been implied between the initial HR deceleration (D1) and the NSW (Connor & Lang, 1969; Rockstroh & Elbert, 1990), and between HR-D2 and the CNV (e.g. Lacey & Lacey, 1970; Simons, 1988). To investigate relations between the cardiovascular and cortical measures in the present study, correlations were computed between the components in the evoked HR and BP patterns and the cortical slow waves. Before carrying out these computations, it was necessary to reduce the amount of data.

First, from the cardiovascular results only the amplitude measures were considered. The latency measures were not used, since the cortical components were measured in fixed epochs. It would not be appropriate to compare the cardiovascular latency measures with cortical amplitudes. The amplitudes from nine phasic cardiovascular components were thus available: HR-D1, HR-A, HR-D2, SBPmin1, SBPmax, SBPmin2, DBPmin1, DBPmax, and DBPmin2. Second, four cortical slow waves were selected. The PSW, NSW, and CNV were taken from the electrode positions where they had the largest amplitude. The PSW was maximal at the parietal, the NSW at the frontal, and the CNV at the central positions. The components from these positions were considered, averaged across the left and the right hemisphere. Furthermore, the CNV at the frontal positions was taken as a measure for the frontal negative slow wave (FSW) used by Skinner, Beckman, & Gray (1987). This slow wave was included in the analysis, because Skinner et al. (1987) found a relation between the amplitude of this slow wave and the number of cardiac arrhythmias in a group of cardiac patients (see also Chapter 1). Five measures of tonic cardiovascular reactivity are used: Mean values of HR, SBP, DBP, RSA (vagal tone), and baroreflex sensitivity (BRS). Finally, the data for these eighteen measures were averaged across memory load (Experiment 1) and KR (all experiments) conditions, whereas the phasic measures were used from the fast instruction trials only.

The number of subjects with complete phasic and tonic datasets was 40. From the first, second and third experiment 15, 12, and 13 subjects were included respectively.

5.2.1 Correlations

Table 5.1 presents the correlation coefficients. Because of the large number of correlations, only those significant beyond the 1 % level are taken into consideration to avoid capitalization on chance.

	HR			SBP			DBP			tonic measures					slow waves		
	D1	A	D2	min1	max	min2	min1	max	min2	HR	RSA	SBP	DBP	BRS	PSW	NSW	FSW
HR-D1	1																
HR-A	**.49**	1															
HR-D2	**.48**	.30	1														
SBPmin1	−.18	**−.41**	−.34	1													
SBPmax	.14	**.46**	−.08	**.45**	1												
SBPmin2	.37	.39	**.52**	.16	**.62**	1											
DBPmin1	.26	.12	.08	**.50**	**.60**	**.47**	1										
DBPmax	.37	**.68**	.25	−.01	**.77**	**.65**	**.69**	1									
DBPmin2	**.43**	**.50**	**.62**	−.05	**.55**	**.88**	**.58**	**.81**	1								
HR	−.25	.15	**−.51**	.24	**.50**	−.01	.27	.34	.02	1							
RSA	**−.58**	−.24	**−.47**	.19	−.10	**−.44**	−.34	**−.41**	**−.54**	.10	1						
SBP	.06	.24	−.13	−.14	.36	.16	.05	.35	.23	**.47**	−.10	1					
DBP	−.02	.24	−.10	−.04	.37	.22	.06	.31	.22	**.51**	−.04	**.85**	1				
BRS	.03	.13	.15	.06	−.19	−.03	−.24	−.28	−.15	**−.49**	.35	**−.40**	−.28	1			
PSW	.15	.17	−.11	−.12	.05	.09	.17	.23	.13	.00	−.17	.24	.18	−.17	1		
NSW	−.39	−.06	−.37	−.09	.04	−.15	.02	.10	−.07	.26	.07	.20	.11	−.37	**.50**	1	
FSW	.03	.14	.20	−.40	−.11	.13	.03	.15	.23	−.18	−.01	−.01	−.09	−.11	.32	**.45**	1
CNV	−.06	.04	.20	−.30	−.15	.05	−.07	.02	.11	−.29	.19	−.11	−.19	.05	.24	.35	**.82**

Table 5.1: *Correlations between the phasic cardiovascular and cortical, and the tonic cardiovascular measures ($N = 40$). The measures are averaged across all conditions, but only for the instruction to give a fast response. The significant correlations ($p < 0.01$) are highlighted.*

The first category of correlations contains those among the phasic cardiovascular components. The significant correlation of HR-D1 with HR-A and HR-D2 suggests that part of the evoked HR pattern is determined by the change that occurs immediately after S1; the larger the initial deceleration, the smaller is the amplitude of the subsequent maximum, and the larger the amplitude of D2. In the BP patterns, too, the amplitudes of the later components are related to the initial change, as shown by the significant correlations between SBPmin1 and -max, SBPmax and -min2, DBPmin1 and both -max and -min2, and between DBPmax and -min2. The correlations among the SBP and DBP components are obviously rather high, since they are related by nature. Only the initial components (SBP- and DBPmin1) show weak correlations with the other components. This is probably due to the effect of overlap with previous trials, which was discussed in Chapter 3 (section 3.4).

Positive correlations were expected between the components of HR and BP; HR-D1 with BPmin1, HR-A with BPmax, and HR-D2 with BPmin2. The first of these expected correlations was not found; HR-D1 correlated only weakly with the initial BP decrease. This result is probably due to the overlap with the previous trial in the BP patterns; since the evoked BP patterns are slower, the changes evoked in the previous trial may not have disappeared when the present trial started. In the HR pattern this effect is probably much smaller, which may cause the dissociation between the initial HR and BP components. HR-A did show the expected positive correlation with SBP- and DBPmax. However, also a negative correlation between HR-A and SBPmin1 was found, which suggests that a larger HR-A is associated with a larger SBPmin1, i.e. the increase in HR is proportionally related to the decrease in SBP which occurs at about the same time. Finally, there were reasonably high correlations between HR-D2 and SBP- and DBPmin2. Although other combinations were significant as well, the overall pattern of results shows that HR-D1 should be associated with SBP- and DBPmin1, HR-A with SBP- and DBPmax, and HR-D2 with SBP- and DBPmin2.

The second category of correlations are between the components of evoked HR and BP on the one hand, and the tonic cardiovascular measures on the other. The (negative) correlation between the average level of HR and the HR-D2 component suggests that the higher one's HR, the larger the phasic deceleration. This result reminds of the law of initial values: the higher the absolute level, the more it can change. An interesting series of significant correlations is found between RSA and HR-D1, HR-D2, SBPmin2, DBPmax, and DBPmin2, which associate higher levels of RSA (vagal tone) with larger HR decelerations, larger BP decreases, and a smaller DBP increase. These results appear to be in line with the earlier discussion on the autonomic origin of the evoked cardiovascular changes (see section 5.1.3) that decreases are predominantly of vagal origin, and increases occur due to a relative increase of sympathetic activity.

Within the cluster of tonic cardiovascular measures significant correlations are found between HR and both SBP and DBP, which indicate that high HR is asso-

ciated with high BP. The correlation of both HR and SBP with BRS shows that high levels of HR and SBP are associated with low levels of baroreflex sensitivity. The implications of this association will be discussed later on (section 5.2.3).

Finally, the correlations between the cortical slow waves and the cardiovascular measures appear to give a random pattern of results; none of these correlations was significant beyond the 1 % level. Marginally significant ($p < 0.05$) correlations were found between HR-D1 and the NSW, between HR-D2 and the NSW, and between SBPmin1 and the FSW. The correlations between the HR decelerations and the NSW were opposite to those found by Connor & Lang (1969), who reported correlations around between 0.43 and 0.66 between the NSW and the three components of the evoked HR response. The low correlation between the CNV and HR-D2 ($r = 0.20$) is about the same as found by Otten et al. (1995) ($r = 0.15$). Van der Veen (1997) also did not find significant correlations between cardiovascular and cortical measures. The present results suggest that there is no relation between the cardiovascular and cortical measures.

5.2.2 Factor analysis

An additional way of looking at relations among the variables is by means of a factor analysis. All variables which were used in the correlational analysis above were used. Table 5.2 gives a review of the factor loadings. Only factors with an eigenvalue larger than 2 were included. Together, these three factors explain about 61 % of the variance.

The three factors generally make a distinction between phasic cardiovascular variables (HR-D1, -A, and D2, SBPmax and -min2, and DBPmin1, -max, and -min2), tonic cardiovascular variables (HR, SBP, DBP, and BRS), and cortical components (PSW, NSW, FSW, CNV). The fact that these variables are assigned to three different factors is a further indication that the measures are weakly related. The first factor (phasic cardiovascular) also includes the RSA measure; the correlations in Table 5.1 also showed that a larger RSA is accompanied by larger phasic decreases of HR and BP. The seconds factor (tonic cardiovascular) includes HR-D2, SBPmax, and the NSW. In the correlation table, HR-D2 was negatively correlated with tonic HR, SBPmax was positively correlated with HR, and also with the tonic SBP and DBP levels. The relation between the NSW and the tonic cardiovascular levels was less clear. Finally, the third, cortical factor includes SBPmin1. Above, correlations between SBPmin1 and the late slow waves (FSW and CNV) were found to be marginally significant ($p < 0.05$), with larger slow waves being associated with a smaller amplitude of SBPmin1.

In conclusion, the factor analysis confirms the results of the correlational analysis, that the relations between cortical and cardiovascular components, if they exist, cannot be revealed in this type of study. On the other hand, since there were only 40 subjects in these analyses, the variance within this group of subjects may be too large to find existing relations. Furthermore, the cardiovascular and

Factor 1		Factor 2		Factor 3	
eigenvalue	5.07		3.28		2.66
% expl.var.	28.2		18.2		14.8
HR-D1	.70	HR-D2	−.50	SBPmin1	.66
HR-A	.63	SBPmax	.60	PSW	.51
HR-D2	.68	NSW	.54	NSW	.57
SBPmax	.53	HR	.82	FSW	.86
SBPmin2	.84	SBP	.71	CNV	.79
DBPmin1	.56	DBP	.68		
DBPmax	.79	BRS	.60		
DBPmin2	.91				
RSA	.65				

Table 5.2: *Factor loadings of phasic cardiovascular and cortical components and tonic cardiovascular measures. Only loadings* > 0.50 *are shown.*

cortical measures which were used in the present study are all indirect measures. For instance, the measurement of brain activity takes place with electrodes attaches at the outside of the scalp. The activity of a particular brain area is thus measured through other brain areas, the skull, skin, hair, electrode paste, electrode, etc. The accuracy of electrode placement also is a source of disruption, not to mention individual differences in anatomy (size of the head, (a)symmetry of the brain, etc.). Similar problems arise in the blood pressure measurement, which takes place at the finger. Thus, apart from individual variations in cortical and cardiovascular reactivity, numerous other factors may have played a role in finding, or rather, not finding significant correlations.

As a last attempt to identify cortical-cardiovascular relations it might be useful to make a subdivision of the subjects into different groups. For instance, Otten (1991) pre-selected subjects who scored either very high or very low on trait-anxiety. In the low-anxious subjects the PSW was highly correlated with phasic BP increase, whereas these correlations were low in the high-anxious subjects. This implies that the experimental population may consist of subgroups with differential results. The following section presents the results of this investigation.

5.2.3 Large versus small FSW

Skinner et al. (1987) found a relation between the amplitude of the frontal negative slow wave (FSW) and the number of cardiac arrhythmias in cardiac patients. This suggests that the frontocortical activity, as expressed in the FSW, may be responsible for the occurrence of arrhythmias. Although the task used by Skinner et al. (1987) was rather different than the tasks used in the present study, it would be interesting to see whether in the normal subjects used in the present

study the frontal cortical negativity (FSW) would be related to cardiovascular reactivity. For this purpose, the 40 subjects with complete datasets were divided into three groups. The subjects in Group 1 have a large average FSW, the subjects in Group 3 have a very small FSW (the average is slightly positive), and the subjects in Group 2 have an intermediate FSW.

Statistical comparison Table 5.3 gives an overview of the three groups. Statistical comparisons will be made between the extremes, i.e. Group 1 and Group 3. These groups consist of 15 subjects, to improve statistical power. The intermediate group consists of 10 subjects.

For the comparison, the same slow wave measures were used as in Chapter 4; the S1-S2 interval is divided into twelve epochs of 0.5 s, except for the first (PSW) which is only 300 ms, starting at 200 ms after S1. The patterns of HR and BP are also divided into 0.5 s epochs, for the entire analysis interval from S1 until ten seconds after. For each of the epochs t-tests are used to reveal the statistical difference between the groups. Furthermore, the latency and amplitude of the components of the HR and BP responses were compared as well; HR-D1, -A, and -D2, SBPmin1, -max, and -min2, and DBPmin1 and -min2.

	Group 1	Group 2	Group 3
N	15	10	15
FSW	−9.2	−4.2	+0.7
standard deviation	3.7	0.7	2.9
minimum	−20.0	−5.2	−3.0
maximum	−5.4	−3.3	+8.0

Table 5.3: *Three groups of subjects, selected by the amplitude of the FSW.*

Phasic and tonic group differences Figure 5.2 presents the average cortical and cardiovascular patterns of each of the groups. The difference between the cortical patterns is obviously quite large, since this was the selection criterion. At the frontal positions, the difference between Group 1 and Group 3 is significant for the entire S1-S2 interval. At the central and parietal positions the difference between Group 1 and Group 3 is significant from about 2 seconds after S1 until S2.

The patterns of evoked HR and BP are different too. The comparisons reveal that Group 1 has only a very small accelerative HR component which does not exceed baseline, and appears to have a stronger deceleration. Between 4.5 and 8.5 seconds after S1 the difference between Group 1 and Group 3 is marginally significant ($p < 0.10$), with a significantly larger deceleration around S2 ($p < 0.05$). The component analyses showed that the latency of HR-D1 was longer

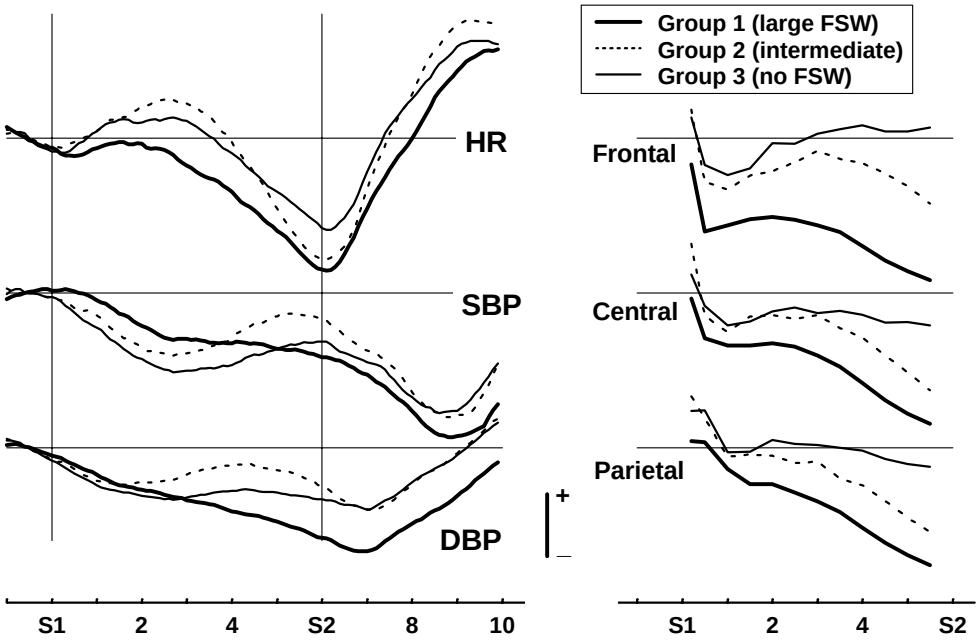

Figure 5.2: *Average HR, SBP, and DBP responses and cortical slow waves in three groups of subjects. Group 1 has a large frontal cortical negativity, Group 2 an intermediate, and Group 3 has a very small frontal negativity. The height of the bar represents 2 bpm, 2 mmHg, and 4 μV for HR, BP, and the slow waves, respectively.*

in Group 1 (735 ms) than in Group 3 (450), and that the amplitude of HR-D2 tended to be larger in Group 1 (−4.5 bpm, vs. −3.2 in Group 3, $p < 0.10$). These effects are significant with $p < 0.05$.

In the BP responses it is clear that in Group 1 there is virtually no increase; the BP mainly decreases until just the occurrence of the 'second' decrease (BPmin2). In contrast, the BP patterns for Group 3 are triphasic; after the initial decrease there is a slight increase of BP before the second decrease is initiated. The SBP pattern shows that Group 3 has a strong initial decrease, and Group 1 a rather small one; until 3 seconds after S1 this difference is significant ($p < 0.05$). The later differences between the patterns are not significant. The peak analyses show that the amplitude of SBPmin1 was larger in Group 3 (−3.1 mmHg) than in Group 1 (−2.2), and that the latency of SBPmin2 was longer in Group 1 (8.9 s, vs. 8.6 in Group 3).

The DBP patterns differ only in the last part of the evoked response; in the four seconds after S2 the difference between Group 1 and Group 3 is significant ($p < 0.05$). The amplitude of DBPmin2 was larger in Group 1 (−3.5 mmHg) than in Group 3 (−2.3).

These phasic group differences suggest that in the group with large fronto-

cortical reactivity, i.e. a large FSW, there is a larger phasic autonomic reactivity. The evoked HR pattern suggests that the increase of vagal outflow is larger than in the group with a small FSW, and the evoked BP patterns suggest that this is accompanied by a larger decrease in sympathetic activity. These results are similar to the results of Van der Veen (1997), who used the same grouping of subjects.

Although the average phasic responses between the groups looked rather different, the average tonic cardiovascular levels during the task did not differ between the groups. A similar result was found by Rockstroh & Elbert (1990), who investigated a group of patients with bilateral frontal lobe lesions. These patients showed less pronounced evoked cardiac responses than healthy control subjects, although their mean tonic levels of HR did not differ. These results may indicate that not the absolute tonic levels are the relevant measures here, but that cardiovascular reactivity should be measured. Thus, it may be relevant to investigate the change in the tonic levels during task performance, relative to a 'baseline' situation in which no task is performed.

Tonic reactivity Before the first task was performed in each experiment, the subjects sat quietly for ten to fifteen minutes to adapt to the situation. During this period, the physiological measurement had started to obtain a baseline measurement. The tonic cardiovascular levels from this period are now used to compare the groups. Figure 5.3 gives an overview of the reactivity of the tonic levels.

The tonic cardiovascular reactivity was investigated in an ANOVA, with the between-subjects factor group (Group 1 versus Group 3), and the within factor period (baseline or task). Table 5.4 gives an overview of these ANOVAs. The groups differed on HR. Group 1 had a higher baseline level of HR than Group 3, and only Group 3 showed a significant increase from baseline to task. The RSA increased relative to baseline in both groups; the marginally significant group $\times$ period interaction showed that in Group 3 the increase was not significant. The levels of SBP and DBP showed similar increases from baseline to task in each of the groups. The BRS increased from baseline to task, but this increase was significant only in Group 1; the baseline level in Group 1 was lower than in Group 3.

	HR	RSA	SBP	DBP	BRS
Group	1.5	< 1	< 1	1.1	< 1
Period	< 1	16.8***	35.8***	26.2***	7.0*
G $\times$ P	6.4*	3.5	< 1	1.4	4.2*

Table 5.4: *Overview of the F-values of* ANOVA *comparisons of tonic cardiovascular reactivity.* $df = 1, 28$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

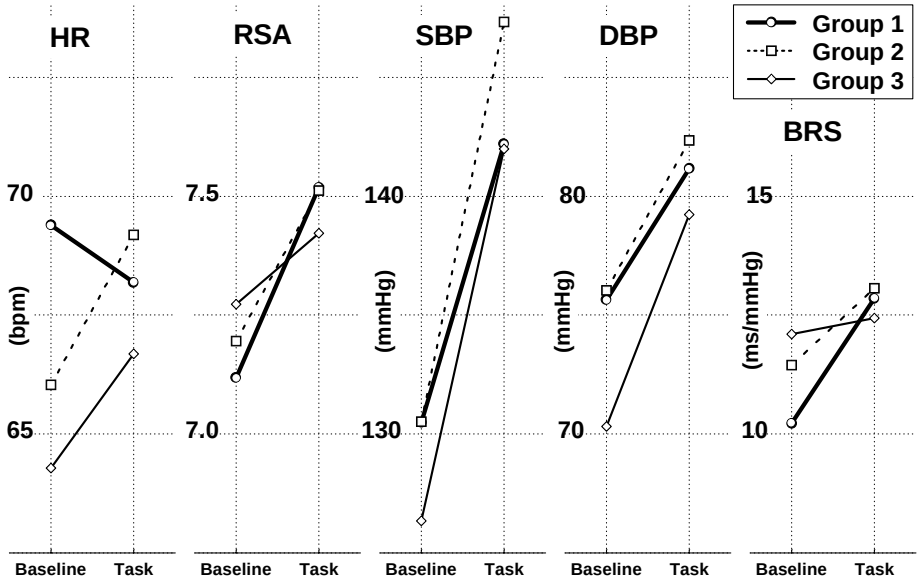

Figure 5.3: *Tonic cardiovascular reactivity in the three groups of subjects. Group 1 has a large FSW, Group 2 intermediate, and Group 3 has no FSW.*

These results show that the tonic reactivity did tend to differentiate the subjects with a large FSW and with a very small (or absent) FSW. The subjects with a large FSW (Group 1) had higher baseline level of HR and lower level of BRS. Note that the correlations in Table 5.1 also showed that high heart rates were associated with low BRS. Group 1 did not change their HR during task performance, but increased the BRS, whereas Group 3 increased their HR and did not change BRS. Furthermore, although the interaction was only marginally significant ($p < 0.10$), the increase in vagal tone (RSA) was larger in Group 1. The groups showed similar rises in SBP and DBP.

5.2.4 Discussion

Skinner et al. (1987) found more cardiac arrhythmias in subjects with larger FSWs. In the light of the present results this would imply that the subjects in Group 1 would have a higher cardiovascular risk. Having a higher HR and a lower baroreflex sensitivity (BRS) in the baseline period could indicate that these subjects have a more vulnerable cardiovascular system. In general, a high baseline BRS is assumed to be healthy; Schwartz, Vanoli, Stramba-Badiale, De Ferrari, Billman, & Foreman (1988) showed that dogs with a high BRS were less vulnerable for cardiac fibrillation than dogs with low BRS. Thus, a low BRS could be considered a sign of higher risk. Furthermore, a high level of HR variability is considered healthy; many cardiac patients have been shown to have relatively

low levels of HR variability (e.g. Kleiger, Miller, Bigger, Moss, & the Multicenter Post-Infarction Research Group, 1987; Casolo, Balli, Taddei, Amuhashi, & Gori, 1989). A larger HR variability indicates a higher vagal tone (here: RSA, an index of vagal tone). A low level of HR variability (RSA) thus suggests a relatively low vagal tone. Furthermore, a high absolute level of HR may also be a sign of relatively low vagal tone (or relatively high sympathetic tone). This suggests that the subjects in Group 1 might have a relatively higher risk for cardiac vulnerability than the subjects in Group 3.

However, when the subjects of Group 1 performed the task, their vagal tone (RSA) increase stronger than in Group 3, and the BRS increased as well. These changes might just as well indicate that these subjects are very well capable of adjusting their cardiovascular system in a 'safe' way, particularly when it is noted that vagal activity is mostly seen as protective (e.g. Verrier & Lown, 1982), and sympathetic as threatening. It appears that the increase in vagal tone antagonizes sympathetic effects; this may explain why the rise in tonic BP is the same as in Group 3, whereas HR does not change: The rise in BP is caused by an increase in sympathetic activity. This increase in sympathetic activity would have caused an increase in HR as well, but the simultaneous increase in vagal tone appears to have compensated for this effect.

The subjects in Group 3 have a lower baseline level of HR, but both HR and BP are increased during task performance. Here, the increase in sympathetic activity during task performance appears not to be compensated for by a simultaneous increase in vagal tone. Although the vagal tone (RSA) slightly increased, this rise was not strong enough to compensate for the sympathetic effect. The subjects in Group 3 thus appear to have a different balance of vagal and sympathetic tone, with sympathetic activity becoming more influential during task performance. The phasic cardiovascular patterns appear to confirm these results; Group 1 did not have the intermediate increase in HR and BP, which was hypothesized to be largely of sympathetic origin. In contrast, Group 3 shows these increased HR and BP components very clearly, which is due to the relatively larger sympathetic than vagal activity.

In summary, the results appear to partly confirm and partly reject Skinner et al.'s (1987) hypothesis. The subjects who display a large FSW appear to have less 'healthy' baseline cardiovascular levels. Their baseline level of HR is relatively high, and RSA and BRS are relatively low. However, their reactivity during task performance appears to mobilize protective, vagal activity which compensates for the increase in sympathetic activity. In contrast, in the subjects who have only a very small FSW, the baseline levels of cardiovascular measures appear to be more satisfactory, i.e. lower HR, higher RSA and BRS, but during task performance the hypothesized harmful activity of the sympathetic branch of the autonomic nervous system has a large influence, and is not compensated for by vagal activity.

The question now becomes: what is a larger risk factor for cardiac vulnerabil-

ity? With a large FSW a person appears to be less well off when the baseline levels are considered, but their reactivity shows that adaptation to a new situation generates protective vagal activity. On the other hand, a person with a small FSW has more satisfactory baseline levels, but reacts inadequately, with a relatively large sympathetic outflow, to a change. Or perhaps it should be concluded that it is best not to stand out in any direction, but to stay safely in the middle. The subjects in Group 2, with the intermediate FSWs, had a relatively low baseline HR, and intermediate levels of RSA and BRS. However, in their reactivity they displayed what appears to be a well-balanced outflow of both sympathetic (HR and BP increase similar to Group 3) and vagal (RSA and BRS increase similar to Group 1) activity. The conclusion should probably be that no conclusions can be drawn from the present results. However, an interesting difference was found between 'normal', 'healthy' subjects, which may trigger further research into the relation between frontocortical activity and cardiovascular reactivity.

5.3 Conclusions

Before listing the main findings and conclusions of this thesis, first an observation should be made regarding the methods used. There are many possible ways to investigate cardiovascular-cortical relations. Due to some restrictions which are inherent to psychophysiology (e.g. only noninvasive measures can be used, and preferably human subjects should be studied), the number of measures is limited. The present study decided to use, initially, phasic measures of both cortical and cardiovascular reactivity. Although the phasic cardiovascular measurements have resulted in a large amount of interesting new data, the relations with the cortical measures were inconclusive. The assignment of the subjects to different groups, with either a large or a very small frontal cortical negativity, appeared to give better relations, but mainly with the tonic cardiovascular measures.

Below, the main findings and conclusions are presented.

Two methods with the same result The mostly used method for deriving evoked HR response from raw HR data is linear interpolation, even though the theoretical rationale behind this method is weak. The results presented in this thesis show that the linear interpolation method gives the same results as a low pass filtering method, which stems from a theoretical model for the generation of heart beats.

Phasic cardiovascular results The first main conclusion is that the classical triphasic pattern of the evoked HR response is accompanied by a consistent BP pattern. The BP patterns are delayed relative to HR, but have a similar morphology: an initial decrease is followed by an increase and a second decrease. The

intermediate increase is rather shallow, and cannot be detected very accurately in the DBP response.

Phasic changes and input processes The results show that the early components in the evoked HR and BP pattern, as well as the early cortical slow waves reflect effects of processing requirements (memory load). HR-D1 and the initial BP decrease, as well as the PSW, appear to be related to the early parts of stimulus processing, such as perception. HR-A, the BP increase, and the NSW appear to be related to further processing, i.e. processing of the information content of the stimulus. The initial changes are mostly of vagal origin, whereas the HR-acceleration and BP-increase are due to sympathetic activity. The attentional control mechanism related to input processes in the framework of Pribram & McGuinness (1975) is arousal. Neurophysiological evidence shows that arousal, through the neurotransmitters norepinephrine and serotonin, may be related to both sympathetic and vagal activity.

Phasic changes and output processes The late components of evoked HR and BP, as well as the cortical CNV measure, are closely related to the timing and execution of the response. These components are associated with the activation of Pribram & McGuinness (1975). This attentional control mechanism was associated with the neurotransmitter dopamine, which is related to motor processes.

Phasic effects of KR The KR manipulations did not induce lateralization. However, they did appear to affect motivation. The KR manipulations may have affected the third attentional control system of Pribram & McGuinness (1975), effort. The effort system is able to change level setting in the brain, and thus influence sensitivity. Structures involved in effort have been shown to be part of the emotional motor system (Holstege, 1991), which has also been associated with gain and level setting. The effects of KR may thus originate from the change of the sensitivity of certain regulatory mechanisms.

Correlations No significant correlations were found between phasic cardiovascular and cortical components. Although the experimental results appear to suggests some relationships, these are too small to be of interest. The methods and/or the variables used in this thesis appear no to be suitable for this type of investigation.

Frontal cortical negativity and relations with cardiovascular measures The assignment of the subjects to groups with either a large or a very small frontal cortical negativity (FSW) revealed clear differences in cardiovascular reactivity.

Subjects with a large FSW had higher baseline HR, and lower baroreflex sensitivity. They did not change their HR during task performance, but increased the RSA and BRS. These subjects have relatively low baseline levels of vagal activity (or relatively high levels of sympathetic activity), but can mobilize vagal activity when necessary. On the other hand, subjects with a small FSW had a relatively low baseline HR, and high BRS. These subjects displayed an increase in HR during task performance, but did not change the RSA and BRS. These subjects have relatively high baseline levels of vagal tone, but during task performance cannot compensate for the increase in sympathetic activity.